Pain and severe sleep disturbance in the general population:

Primary data and meta-analysis from 240,820 people across 45 low- and middle-income countries

Brendon Stubbs*[1,2], Davy Vancampfort[3,4], Trevor Thompson[5], Nicola Veronese[6,7], Andre F. Carvahlo[8], Marco Solomi[7,9], James Mugisha[10,11], Patricia Schofield[12], A. Matthew Prina[13], Ai Koyanagi[14,15]

Submission to General Hospital Psychiatry

1. Physiotherapy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AZ, United Kingdom
2. Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London, Box SE5 8AF, United Kingdom
3. KU Leuven Department of Rehabilitation Sciences, Leuven, Belgium
4. KU Leuven, University Psychiatric Center KU Leuven, Leuven-Kortenberg, Belgium
5. Faculty of Education and Health, University of Greenwich, London, United Kingdom
6. Geriatrics Division, Department of Medicine-DIMED, University of Padova, Italy
7. Institute of Clinical Research and Education in Medicine (IREM), Padova, Italy
8. Translational Psychiatry Research Group and Department of Clinical Medicine, Faculty of Medicine, Federal University of Ceara, Fortaleza, CE, Brazil
9. Department of Neurosciences, University of Padova, Padova, Italy
10. Kyambogo University, Kampala, Uganda
11. Butabika National Referral and Mental Health Hospital, Kampala, Uganda

12. Faculty of Health, Social Care and Education, Anglia Ruskin University, Chelmsford, United Kingdom
13. Centre for Global Mental Health, Health Service and Population Research Department, Institute of Psychiatry, Psychology & Neuroscience, King's College London, De Crespigny Park, London, SE5 8AF, United Kingdom
14. Research and Development Unit, Parc Sanitari Sant Joan de Déu, Universitat de Barcelona, Fundació Sant Joan de Déu, Dr. Antoni Pujadas, 42, Sant Boi de Llobregat, Barcelona 08830, Spain
15. Instituto de Salud Carlos III, Centro de Investigación Biomédicaen Red de Salud Mental, CIBERSAM, Monforte de Lemos 3-5 Pabellón 11, Madrid 28029, Spain

* **Corresponding author**: Brendon Stubbs, Head, Physiotherapy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill, London, United Kingdom. Tel: 0044 208 3003100, fax 00442032282702 email: brendon.stubbs@kcl.ac.uk

Abstract (247/ 250)

Objective

Pain and sleep disturbances are widespread, and are an important cause of a reduced quality of life. Despite this, there is a paucity of multinational population data assessing the association between pain and sleep problems, particularly among low- and middle-income countries (LMICs). Therefore, we investigated the relationship between pain and severe sleep disturbance across 45 LMICs.

Method

Community-based data on 240,820 people recruited via the World Health Survey were analyzed. Multivariable logistic regression analyses adjusted for multiple confounders were performed to quantify the association between pain and severe sleep problems in the last 30 days. A mediation analysis was conducted to explore potential mediators of the relationship between pain and severe sleep disturbance.

Results

The prevalence of mild, moderate, severe, and extreme levels of pain was 26.0%, 16.2%, 9.1%, and 2.2% respectively, whilst 7.8% of adults had severe sleep problems. Compared to those with no pain, the odds ratio (OR, 95% CI) for severe sleep problems was 3.65 (3.24-4.11), 9.35 (8.19-10.67) and 16.84 (13.91-20.39) for those with moderate, severe and extreme pain levels respectively. A country wide meta-analysis adjusted for age and sex demonstrated a significant increased OR across all 45 countries. Anxiety, depression and stress sensitivity explained 12.9%, 3.6%, and 5.2%, respectively, of the relationship between pain and severe sleep disturbances.

Conclusion

Pain and sleep problems are highly co-morbid across LMICs Future research is required to better understand this relationship. Moreover, future interventions are required to prevent and manage the pain and sleep disturbance comorbidity.

Key words: sleep, pain, sleep disturbance, psychiatry, low- and middle-income countries

Introduction

Sleep disturbance is widespread, and is a potential cause of mental and physical health problems as well as a reduced quality of life [1]. Population cohort studies have demonstrated that sleep deprivation and sleep disorders affect many more people worldwide than previously thought [2]. For example, in a large-scale community-based survey, 'some insomnia problems over the past year' were reported by more than 30% of adults, and chronic insomnia by about 10% [3]. Furthermore, sleep problems are significant predictors of obesity, diabetes, stroke, coronary heart disease, widespread pain and premature mortality [4-9], and increase the risk for the onset of mental disorders such as depression, anxiety disorders and substance misuse [10-12].

Insomnia and sleep disturbances are also a major problem to many people living with chronic pain [8]. The worldwide chronic pain prevalence in the general adult population has been reported to be 30.3% with back pain, headaches and lower extremities pain being the most frequently reported painful ailments [13]. To date, most of the research investigating the relationship between pain and sleep disturbances have focused on high-income countries. For example, in a population-based, cross-sectional telephone survey of 5001 adults aged ≥18 years from the Hong Kong general population, the overall prevalence of people reporting chronic pain, sleep problems and fatigue was 5.6% (95% CI: 4.9-6.4) [14].

Previous studies have shown that the association between sleep problems and pain may be bidirectional. For example, pain may cause insomnia via bodily discomfort during the night and lack of physical activity during the day, while insomnia may lead to pain via central processes that regulate pain signaling at supraspinal and spinal levels [15]. Next to this, shared common risk factors such as physical health conditions, stress, and anxiety and depression have also been suggested [8]. However, the degree to which the relationship between pain and sleep problems is influenced by psychological and psychiatric symptoms (e.g., depression,

anxiety, stress sensitivity) and lifestyle factors (e.g. physical activity participation) remains unclear.

In addition, there is a distinct gap in the literature regarding the association between pain and sleep problems in representative samples of low- and middle-income countries (LMICs). Such data would be valuable as both conditions are highly pervasive among people in LMICs. For example, large multi-national studies from LMICs reported the prevalence of severe sleep problems to be 7.6%, ranging from 1.6% (China) to 18.6% (Morocco) (n=261,547 individuals aged ≥ 18 years from 56 countries) [16], while the overall age–sex adjusted prevalence of severe pain was 11.1%, ranging from 1.7% (China) to 31.3% (Morocco) (n= 235,370 individuals aged ≥ 18 years from 44 countries) [17]. The association between pain and sleep problems in LMICs may however differ from high-income settings owing to factors such as differences in disease profiles which may cause pain and sleep problems, suboptimal treatment for physical and mental health conditions, inadequate pain control, and limited availability of non-pharmacologic or pharmacologic treatment for insomnia [2,18,19]. To the best of our knowledge, only one large-scale multi-country in LMICs has previously investigated sleep problems and pain specifically in the elderly (≥65 years) [20]. This study found that pain severity was a good predictor for reporting sleep complaints, with prevalence ratios ranging from 1.232 (95% CI = 1.02–1.48) for mild pain in the Dominican Republic to 4.261 (95% CI = 2.84–6.40) for unbearable pain in India. Whilst the paper advance the field, only eight countries (n= 16,680) were included in the analysis, data were not nationally-representative (only conducted within catchment sites) and it was restricted to older individuals.

Given the current limitations of the literature (few association studies, often with low sample size & poor generalizability), this study aims to: (1) explore the relationship between pain and severe sleep problems across adults aged 18 and over using nationally-

representative data from 45 LMICs; (2) investigate the factors that might influence the relationship between pain and severe sleep problems; and (3) conduct a country-wide meta-analysis to explore if the association between pain and sleep problems are similar across all countries included in the study.

Methods

The current study uses data from the World Health Survey (WHS). The WHS is a cross-sectional, community-based study undertaken in 2002-2004 in 70 countries worldwide. The details of the survey are provided elsewhere (http://www.who.int/healthinfo/survey/en/). Data were acquired using single-stage random sampling and stratified multi-stage random cluster sampling in 10 and 60 countries respectively. People aged ≥18 years with a valid home address were eligible to participate. Each member of the household had equal probability of being selected with the use of Kish tables. Regardless of the country, data were collected using the same standard set of questionnaires, although some countries had a shorter version (and consequently less data). In order to maximize understanding and comparability, the questionnaire was translated into multiple languages and was back- and forward-translated, and checked by linguists. Data collection was conducted either by face-to-face interviews or via telephone by trained interviewers. The mean individual response rate across all countries was 98.5% [21]. Sampling weights were generated to adjust for non-response and the population distribution as reported by the United Nations Statistical Division [22]. Ethical approval to conduct this survey was obtained from ethical boards at each study site. Informed consent was obtained from all participants.

Of the 69 countries for which data were publicly available, 24 countries were excluded for the following reasons: 10 countries (Austria, Belgium, Denmark, Germany, Greece, Guatemala, Italy, Netherlands, Slovenia, UK) due to lack of sampling information, 10 high-income countries (Finland, France, Ireland, Israel, Luxembourg, Norway, Portugal, Spain, Sweden, United Arab Emirates) as the focus of this study was on LMICs, and 4 countries (Congo, Mali, Slovakia, and Swaziland) as >25% of data on the main variables of interest (sleep and/or pain) were missing. Thus, a total of 45 countries were included in the

final analytical sample. According to the World Bank classification in 2003, these countries corresponded to 19 low-income and 26 middle-income countries. The total sample size was 240,820. However, for some analyses, Brazil (n=5000), Hungary (n=1419), Latvia (n=929), Morocco (n=5000), Turkey (n=11481), or Zimbabwe (n=4290) were omitted due to missing data for some of the variables used in the analysis. The data were nationally-representative for all countries with the exception of China, Comoros, Ivory Coast, India, and Russia.

Variables

Severe sleep problems (outcome variable)

For the purposes of the current study, severe sleep problems were assessed according to the question "Overall in the last 30 days, how much of a problem did you have with sleeping, such as falling asleep, waking up frequently during the night or waking up too early in the morning?". The answer options were none, mild, moderate, severe, and extreme. Participants who answered severe and extreme were considered to have severe sleep problems. This definition has been used in previous publications using the same survey question on sleep problems [16,23,24].

Pain (exposure variable)

Pain was assessed in two ways. Participants were asked "Overall in the last 30 days, how much of bodily aches or pains did you have?" with answer options being none, mild, moderate, severe, and extreme. This variable was used as a categorical variable. Second, a continuous pain variable was constructed with the use of the above-mentioned question and another question "In the last 30 days, how much bodily discomfort did you have?" which also had the same response options. A factor analysis with polychoric correlations was used in order to obtain a factor score which was converted into a scale ranging from 0 to 10 with

higher scores corresponding to higher levels of pain/discomfort. These pain scores have previously been used in papers from the WHS [25,26].

Control variables

The control variables were selected based on past literature [16,17], and included sex, age, highest educational level achieved (no formal education, primary education, secondary or high school completed, or tertiary education completed), wealth, setting (rural/urban), current smoking, alcohol consumption, and physical diseases. Principal component analysis based on 15-20 assets was performed to establish country-wise wealth quintiles. The question on smoking was 'Do you currently smoke any tobacco products such as cigarettes, cigars, or pipes?' with the answer options being 'daily', 'yes, but not daily', or 'no, not at all'. This variable was dichotomized into those who smoked regardless of frequency (i.e., daily or not daily) (current smokers) and those who do not smoke. Alcohol consumption was assessed by first asking the question 'Have you ever consumed a drink that contains alcohol (such as beer, wine, etc)?' Respondents who replied 'no' were considered lifetime abstainers. If the respondent replied affirmatively, then he/she was asked how many standard drinks of any alcoholic beverage he/she had on each day of the past 7 days. The number of days in the past week in which 4 (female) or 5 (male) drinks were consumed was calculated, and a total of 1-2 and ≥3 days in the past 7 days were considered infrequent and frequent heavy drinking respectively. All other respondents, apart from lifetime abstainers, were considered non-heavy drinkers [16]. Arthritis, asthma, and diabetes were based solely on self-reported lifetime diagnosis. For angina, in addition to a self-reported diagnosis, a symptom-based diagnosis based on the Rose questionnaire was also used [27]. Chronic back pain was defined as having had back pain (including disc problems) every day during the last 30 days. The total number of these conditions was calculated. Data on education was missing from Turkey.

Mediators

The mediators in the association between pain and severe sleep problems which were considered included depression, anxiety, stress sensitivity, and low physical activity. This was based on past literature pointing to pain leading to these conditions, which in turn, may lead to sleep problems [28-30]. The presence of depression based on the duration and persistence of depressive symptoms in the previous 12 months was established using DSM-IV criteria [16]. Anxiety was assessed by the question "Overall in the past 30 days, how much of a problem did you have with worry or anxiety?" Respondents could answer: none, mild, moderate, severe, or extreme. For the purposes of the current study, participants who answered severe and extreme were categorized as having anxiety [16,31]. Stress sensitivity in the last month was assessed by two questions: "How often have you felt that you were unable to control the important things in your life?"; and "How often have you found that you could not cope with all the things that you had to do?" The answer options to these questions were: never (score=1), almost never (score=2), sometimes (score=3), fairly often (score=4), very often (score=5). The scores of the two questions were added to create a scale ranging from 2 to 10 [32]. The short form of the International Physical Activity Questionnaire was used to assess the level of physical activity using conventional cut-offs (low, moderate, high) [33]. This was dichotomized as low physical activity or else (moderate and high) [34]. Data on depression and anxiety were missing from Turkey and Morocco respectively. Furthermore, there was no data on stress sensitivity from Brazil, Hungary, Turkey, and Zimbabwe, while Latvia and Morocco had no data on physical activity.

Statistical analysis

The statistical analysis was performed with Stata 14.1 (Stata Corp LP, College station, Texas). Descriptive analysis was performed to illustrate sample characteristics across

different levels of pain. Chi-squared tests and one-way ANOVA were used to assess the difference between sample characteristics by different pain levels for categorical and continuous variables respectively. Using the overall sample, multivariable logistic regression analysis was conducted to assess the association between pain (exposure variable) and severe sleep problems (outcome variable). Two different pain measures (mentioned above) were used and were included individually in the models. Stratified analyses by sex and age groups (18-44, 45-64, ≥65 years) were also conducted. The models were adjusted for sex, age, education, wealth, setting, current smoking, alcohol consumption, physical diseases, and country, with the exception of the sex-stratified models which were not adjusted for sex. A test for trend was performed by including the categorical pain variable as a continuous variable in the models.

Next, a mediational analysis was conducted to understand the extent to which the association between pain and severe sleep problems can be explained by the hypothesized mediators (depression, anxiety, stress sensitivity, low physical activity). The *khb* (Karlson Holm Breen) command in Stata [35] was used for this purpose. This method, which can be used with logistic regression models, has been widely applied in mental health research [36], and decomposes the total effect into direct and indirect effects. This method also allows for the calculation of the mediated percentage (percentage of the main association that can be explained by the mediator). Each potential mediator was included in the models separately, and the models were adjusted for sex, age, education, wealth, setting, current smoking, alcohol consumption, physical diseases, and country.

Finally, in order to assess the generalizability of the findings based on the pooled sample across all countries, we conducted country-wise logistic regression analyses for the association between the pain score and severe sleep problems while adjusting for age and sex. A pooled estimate was obtained by meta-analysis with random effects. For all regression

analyses, the variables were included in the models as categorical variables with the exception of age, pain score, stress sensitivity, and number of physical diseases (continuous variables). Adjustment for country was done by including dummy variables for each country as in previous WHS publications [16,21]. The sample weighting and the complex study design were taken into account in all analyses. Results from the logistic regression models are presented as odds ratios (ORs) with 95% confidence intervals (CIs). The level of statistical significance was set at $P<0.05$.

Results

The mean (SD) age of the sample was 38.4 (16.0) years with 50.7% being females (**Table 1**). Overall, the prevalence of mild, moderate, severe, and extreme levels of pain were 26.0%, 16.2%, 9.1%, and 2.2% respectively, whilst 7.8% of the sample had severe sleep problems. Higher levels of pain were associated with female sex, advanced age, lower levels of education and wealth, current smoking, lifetime abstention from alcohol, greater number of physical diseases, depression, anxiety, higher levels of stress sensitivity, and low physical activity. The prevalence of severe sleep problems increased linearly with increasing levels of pain for all age groups, with a particularly high prevalence of severe sleep problems in the oldest age group for extreme pain (66.5%) (**Figure 1**). The distribution of pain levels in each of the sleep categories are shown in **eTable 1** of the Appendix.

Table 1 here

Figure 1 here

Relationship between pain and severe sleep problems

The association between pain and severe sleep problems estimated by multivariable logistic regression is shown in **Table 2**. Based on the categorical pain variable, there was a dose-dependent incremental odds for severe sleep problems with increasing levels of pain. In the overall sample, compared to those with no pain, the OR (95%CI) for severe sleep problems for those with extreme pain was 16.84 (13.91-20.39). Estimates based on the continuous pain score also showed similar trends with a one-unit increase in the pain score (range 0-10) being associated with 1.43 times higher odds for severe sleep problems in the overall sample. For both pain variables, the association between severe sleep problems was similar across females and males. In terms of age groups, a stronger association was observed for younger age groups.

Table 2 here

Mediators of pain and severe sleep problem relationship

Next, for all the mediators assessed, the indirect effect was significant (**Table 3**). However, apart from anxiety (12.9%), only a small proportion of the association between pain and severe sleep problems was explained by these mediators: depression (3.6%), stress sensitivity (5.2%), and low physical activity (0.6%).

Table 3

Meta-analysis of pain and severe sleep problems

Finally, the country-wise analysis showed that the pain score (range 0-10) is significantly and positively associated with severe sleep problems in all the countries studied with the OR (95%CI) ranging from 1.20 (1.07-1.34) in Senegal to 2.05 (1.72-2.45) in Pakistan. The pooled estimate based on a meta-analysis was 1.51 (95%CI=1.47-1.55). These ORs can be interpreted as the change in ORs associated with a one-unit increase in the pain score. The pooled estimates in low-income countries and middle-income countries were 1.53 (95%CI=1.45-1.61) and 1.50 (95%CI=1.45-1.54), respectively. Every country included in the meta-analysis established that increasing levels of pain was associated with severe sleep disturbance.

Figure 2 here

Discussion

General findings

To the best of our knowledge the current study is the first to explore on a multi-national level, the relationship between pain and severe sleep problems in adults aged 18 and over. Our data show that compared to those with no pain, those with extreme pain had a more than 16-fold increased risk (OR=16.84; 95%CI=13.91-20.39) for severe sleep problems. Moreover, our data suggest that as pain severity increases, an incremental increase odds in severe sleep problems was also evident. Our meta-analysis across 45 countries adjusted for age and sex demonstrated that the relationship between increasing levels of pain and severe sleep problems is consistent across all countries. While anxiety appears to account for a reasonable proportion of (mediation of 12.9%) increased severe sleep problems, the potential contribution of depression (3.6%), stress sensitivity (5.2%), and low physical activity (0.6%) appears to be minimal. However, these factors only explain a small amount of this relationship and it may be that other factors not measured in our study contribute to this relationship.

The current data clearly show a strong relation between pain and severe sleep problems. Although the current study was cross-sectional, it might be hypothesized that pain and sleep disturbances mutually reinforce each other. The mechanisms contributing to the sleep-pain relationship are however poorly understood. Several hypotheses have been formulated to explain the possible underlying mechanisms. First, sleep disturbances disrupt pain modulation – central processes that regulate pain signaling (nociception) at supraspinal and spinal levels [15]. As also emotion circuits are highly interconnected with pain modulation circuitries, emotions can up- and down-regulate pain and spinal nociception [37] while emotional arousal due to sleep problems on its turn may compound the problem [38]. Indeed,

this is consistent with our finding that the link between pain and sleep was partially mediated by anxiety. Second, pain medication might disrupt the sleep–wake cycle [39]. Clearly more research is required to better understand the relationship and in particular establish directionality and underpinning mechanisms.

Whilst we noted that there was a consistent relationship between pain and severe sleep problems across both low and middle income countries, both collectively and individually, there was some variation. For instance, in low income countries, a notably high odds ratio was noted in Pakistan, Laos, Myanmar and Vietnam.). Similarly, high levels of comorbidity of pain and severe sleep problems were noted in middle income countries China and Malaysia There is very little published evidence on the association between severe sleep and pain problems in LMICs. Therefore, any explanation across countries currently is highly speculative. Country-related differences are however intriguing and may hold clues to the etiology of severe sleep and pain problems and their treatment across different settings, and certainly warrant further research. When comparing the odds between low and middle income countries, we can speculate that differences cannot be entirely explained by poverty. Potential hypotheses could include differences in access to sleep and pain management (including access to analgesic and sleep medication or non-pharmacological interventions such as physiotherapy[40]. Next this, also differences in a variety of sociocultural factors, from traditional and religious beliefs towards pain and sleep problems to local preferences for sleep and pain management may influence country-wise disparities in the association of pain with severe sleep problems [41].

Our data demonstrates that sleep problems are an important problem in people experiencing pain in LMICs. More research to understand the underlying mechanisms for this relationship is urgently needed. However, even before more rigorous evidence is available, clinicians in practice should be alerted to this high level of association. For example, future research should explore whether systematically integrating sleep assessment, in the clinical practice guidelines for people experiencing acute or chronic pain and vice versa systematically integrating pain assessments in those experiencing severe sleep problems might reduce the co-morbid burden of severe sleep or pain problems. However, effective sleep and pain monitoring will not be not sufficient on its own, as appropriate treatment is also mandatory. Pharmacotherapy of sleep disturbances due to acute or chronic pain has however received very little attention. To date, several drug classes have been evaluated, and no consensus on treating disturbed sleep in acute or chronic pain has arisen [39]. In resource-limited settings, many of the medication used in developed country settings may also not be available [30]. There are, to the best of our knowledge, currently also no evidence-based treatment algorithms for comorbid pain and sleep problems. However, a recent meta-analysis [43] indicated that non-pharmacological sleep treatments (including physiotherapy, exercise, yoga, qigong, mindfulness meditation, massage, and cognitive behavioral therapy involving psychoeducation, sleep hygiene, stimulus control therapy, sleep restriction therapy, sleep scheduling, relaxation, paradoxical intention, and imagery exercises) in chronic pain patients were associated with a large improvement in sleep quality (standardized mean difference = 0.78; 95%CI=0.42 to 1.13, P< 0.001) and a small reduction in pain (SMD=0.18, 95%CI=0 to 0.36, P<0.05) post-treatment. The effects on sleep quality were maintained at follow-up (up to 1 year) when a moderate reduction in depression (SMD=0.31; 95%CI=0.09 to 0.53, P<0.01) was also observed. However, although efficacious in high-income countries, research regarding the effectiveness of these non-pharmacological treatments, including a

cost-effectiveness analysis, in LMICs is urgently needed before any of these therapies can be recommended.

Study limitations

Current findings should be interpreted in the light of some limitations. First of all, the severity and duration of pain and severe sleep problems could not be assessed due to lack of data. Therefore, we were unable to undertake more detailed analyses related to the type or chronicity of participants' sleep problems which might have helped further elucidate the association between severe sleep problems and pain. Second, the study was cross-sectional, therefore cause and effect between pain and severe sleep problems cannot be deduced with certainty. Clearly, future longitudinal research is required to further explore the potential directionality of the outcomes we observed. Third, we did not have information on medication use such as hypnotics or analgesic medication which may have influenced our data. Future research should consider the impact of such medications and other non-pharmacological interventions (e.g. exercise) and how this influences the relationship between pain and severe sleep problems.

In conclusion, our study suggests that pain is associated with substantially increased odds of severe sleep problems. Our data also suggests that severe sleep problems are incrementally increased with pain severity and that mood (in particular anxiety and depression) may partially mediate this relationship. Given the highly comorbid and pervasive nature of pain and sleep disturbance, future research is required to further understand these relationships and population level interventions are needed to address this common problem.

Conflict of interest

BS, DV, TT, AMP, AK, LS none to declare

Acknowledgment

BS receives funding from the National Institute for Health Research Collaboration for Leadership in Applied Health Research & Care Funding scheme. BS is also part funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

AK's work was supported by the Miguel Servet contract financed by the CP13/00150 and PI15/00862 projects, integrated into the National R + D + I and funded by the ISCIII - General Branch Evaluation and Promotion of Health Research - and the European Regional Development Fund (ERDF-FEDER).

AMP was funded by the Medical Research Council (grant number MR/K021907/1)

Table 1 Sample characteristics by different levels of pain

			Overall in the last 30 days, how much of bodily aches or pains did you have?				
Characteristic		Overall	None	Mild	Moderate	Severe	Extreme
Sex	Male	49.3	56.6	47.6	41.2	35.2	31.1
	Female	50.7	43.4	52.4	58.8	64.8	68.9
Age (years)	Mean (SD)	38.4 (16.0)	34.0 (14.0)	39.3 (15.3)	43.5 (17.1)	47.0 (17.2)	47.3 (15.5)
Education[a]	No formal	26.2	21.4	27.1	29.9	38.7	39.5
	≤Primary	31.0	28.8	31.8	33.5	33.5	37.6
	Secondary completed	33.6	39.2	31.8	28.7	22.2	18.0
	Tertiary completed	9.2	10.6	9.3	7.8	5.6	4.9
Wealth	Poorest	20.1	17.9	19.9	23.0	25.7	25.5
	Poorer	20.0	19.0	19.9	21.9	22.6	20.5
	Middle	20.0	20.3	19.9	19.5	19.6	20.1
	Richer	19.9	20.3	21.0	18.3	17.7	18.9
	Richest	20.0	22.6	19.4	17.4	14.4	15.0
Setting	Urban	44.5	45.7	42.7	46.2	40.2	43.2
Current smoking	No	73.0	74.3	72.0	72.6	70.9	70.4
	Yes	27.0	25.7	28.0	27.4	29.1	29.6
Alcohol consumption	Lifetime abstainer	66.9	67.3	66.9	64.2	68.6	71.3
	Non-heavy	28.4	27.6	28.3	31.4	28.3	25.7
	Infrequent heavy	3.6	3.9	3.9	3.4	2.3	2.3
	Frequent heavy	1.0	1.1	0.9	1.1	0.8	0.6
No. of physical diseases[a]	Mean (SD)	0.42 (0.74)	0.18 (0.47)	0.42 (0.67)	0.70 (0.86)	1.05 (0.99)	1.22 (0.83)
Depression[a]	No	93.0	97.4	94.2	88.4	79.5	69.7
	Yes	7.0	2.6	5.8	11.6	20.5	30.3
Anxiety[b]	No	88.4	94.4	91.1	84.3	65.3	50.4
	Yes	11.6	5.6	8.9	15.7	34.7	49.6
Stress sensitivity[c]	Mean (SD)	4.8 (2.2)	4.3 (2.1)	5.0 (2.0)	5.4 (2.1)	5.9 (2.2)	6.4 (1.9)
Low physical activity[d]	No	82.7	85.7	84.0	80.0	71.5	63.6

Yes	17.3	14.3	16.0	20.0	28.5	36.4

Estimates are based on weighted sample. Data are column % with the exception of age and stress sensitivity [mean (SD)].
Data are from 45 countries unless otherwise stated.
[a] 44 countries (Turkey is not included).
[b] 44 countries (Morocco is not included).
[c] 41 countries (Brazil, Hungary, Turkey, and Zimbabwe are not included). Scale ranges from 2-10 with higher scores indicating higher levels of stress sensitivity.
[d] 43 countries (Latvia and Morocco are not included).
All overall differences in sample characteristics by different levels of pain are statistically significant ($p<0.0001$).

Table 2 Association between pain and severe sleep problems (outcome) estimated by multivariable logistic regression

	Overall		Female		Male		Age 18-44 years		Age 45-64 years		Age ≥65 years	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
(a) Overall in the last 30 days, how much of bodily aches or pains did you have?[a]												
None	1.00		1.00		1.00		1.00		1.00		1.00	
Mild	1.72**	[1.51,1.95]	1.59**	[1.33,1.89]	1.86**	[1.54,2.24]	2.01**	[1.70,2.37]	1.38*	[1.10,1.74]	0.96	[0.69,1.35]
Moderate	3.65**	[3.24,4.11]	3.32**	[2.83,3.89]	4.08**	[3.39,4.91]	4.19**	[3.57,4.92]	3.19**	[2.56,3.98]	1.95**	[1.42,2.66]
Severe	9.35**	[8.19,10.67]	8.80**	[7.40,10.46]	9.75**	[7.85,12.11]	10.72**	[8.95,12.83]	7.94**	[6.31,9.99]	5.23**	[3.79,7.23]
Extreme	16.84**	[13.91,20.39]	16.87**	[13.33,21.35]	15.41**	[11.11,21.38]	17.88**	[13.92,22.97]	13.10**	[9.08,18.90]	13.48**	[8.42,21.56]
(b) Pain score (range 0-10)[b]	1.43**	[1.40,1.45]	1.43**	[1.40,1.46]	1.42**	[1.38,1.46]	1.43**	[1.40,1.47]	1.41**	[1.36,1.46]	1.40**	[1.33,1.48]

Abbreviation: OR odds ratio; CI confidence interval

All models are adjusted for sex, age, education, wealth, setting, current smoking, alcohol consumption, physical diseases, and country with the exception of models restricted to females or males which are not adjusted for sex.

The two pain variables [i.e., (a) and (b)] were included separately in the models.

A total of 44 countries were included in the analysis. Turkey was not included as no information on education was available.

[a] Significant test for trend for all models ($p<0.0001$).

[b] Higher scores on the pain scale indicate more severe pain.

* $p<0.01$, ** $p<0.001$

Table 3 Depression, anxiety, stress sensitivity, and low physical activity as mediators in the association between pain score and severe sleep problems

Mediator	Effect	OR (95%CI)	P-value	% Mediated
Depression[a]	Total	1.43 (1.41-1.46)	<0.0001	3.6
	Direct	1.41 (1.39-1.44)	<0.0001	
	Indirect	1.01 (1.01-1.02)	<0.0001	
Anxiety[b]	Total	1.40 (1.37-1.42)	<0.0001	12.9
	Direct	1.34 (1.31-1.37)	<0.0001	
	Indirect	1.04 (1.04-1.05)	<0.0001	
Stress sensitivity[c]	Total	1.47 (1.43-1.50)	<0.0001	5.2
	Direct	1.44 (1.41-1.47)	<0.0001	
	Indirect	1.02 (1.02-1.02)	<0.0001	
Low physical activity[d]	Total	1.42 (1.40-1.45)	<0.0001	0.6
	Direct	1.42 (1.39-1.45)	<0.0001	
	Indirect	1.002 (1.0008-1.003)	0.0017	

Abbreviation: OR Odds Ratio; CI Confidence Interval

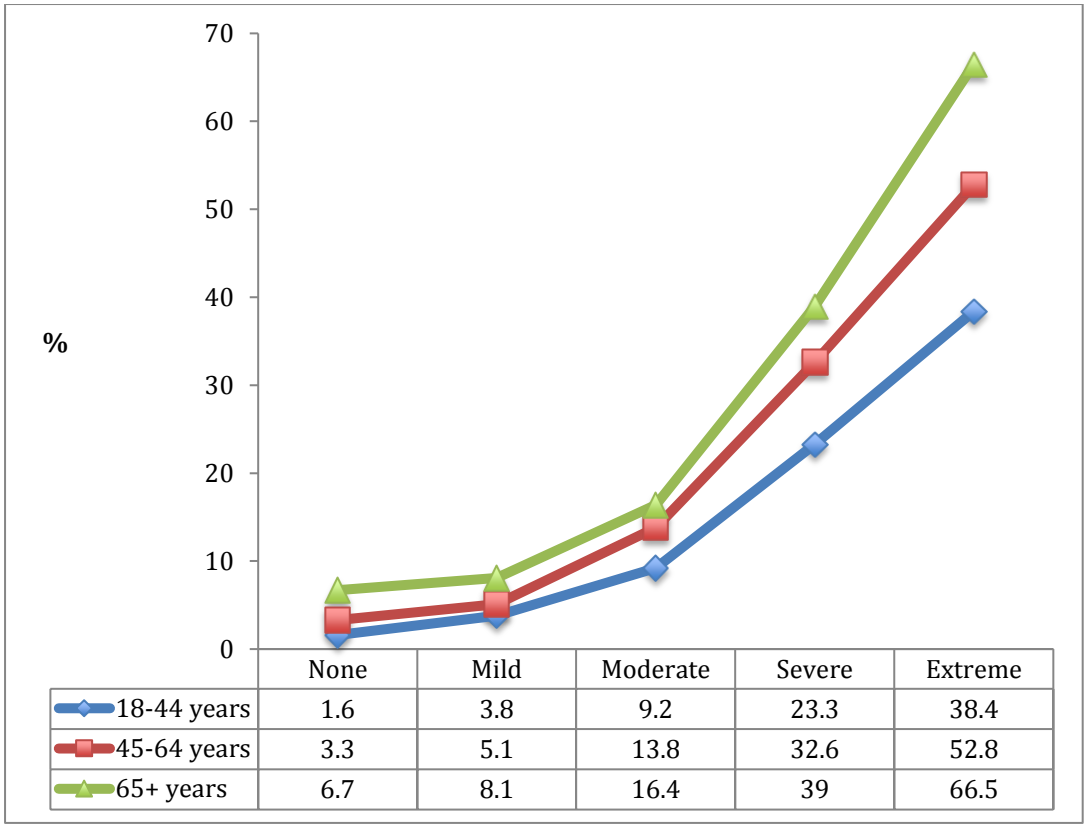
Models are adjusted for sex, age, education, wealth, setting, current smoking, alcohol consumption, physical diseases, and country.

[a] Includes 44 countries (Turkey is not included)

[b] Includes 43 countries (Morocco and Turkey are not included)

[c] Includes 41 countries (Brazil, Hungary, Turkey, and Zimbabwe are not included)

[d] Includes 42 countries (Latvia, Morocco, and Turkey are not included)



	None	Mild	Moderate	Severe	Extreme
18-44 years	1.6	3.8	9.2	23.3	38.4
45-64 years	3.3	5.1	13.8	32.6	52.8
65+ years	6.7	8.1	16.4	39	66.5

Figure 1 Prevalence of severe sleep problems by level of pain and age group
Data is based on weighted sample from 45 countries.
The question used to assess level of pain was "Overall in the last 30 days, how much of bodily aches or pains did you have?"

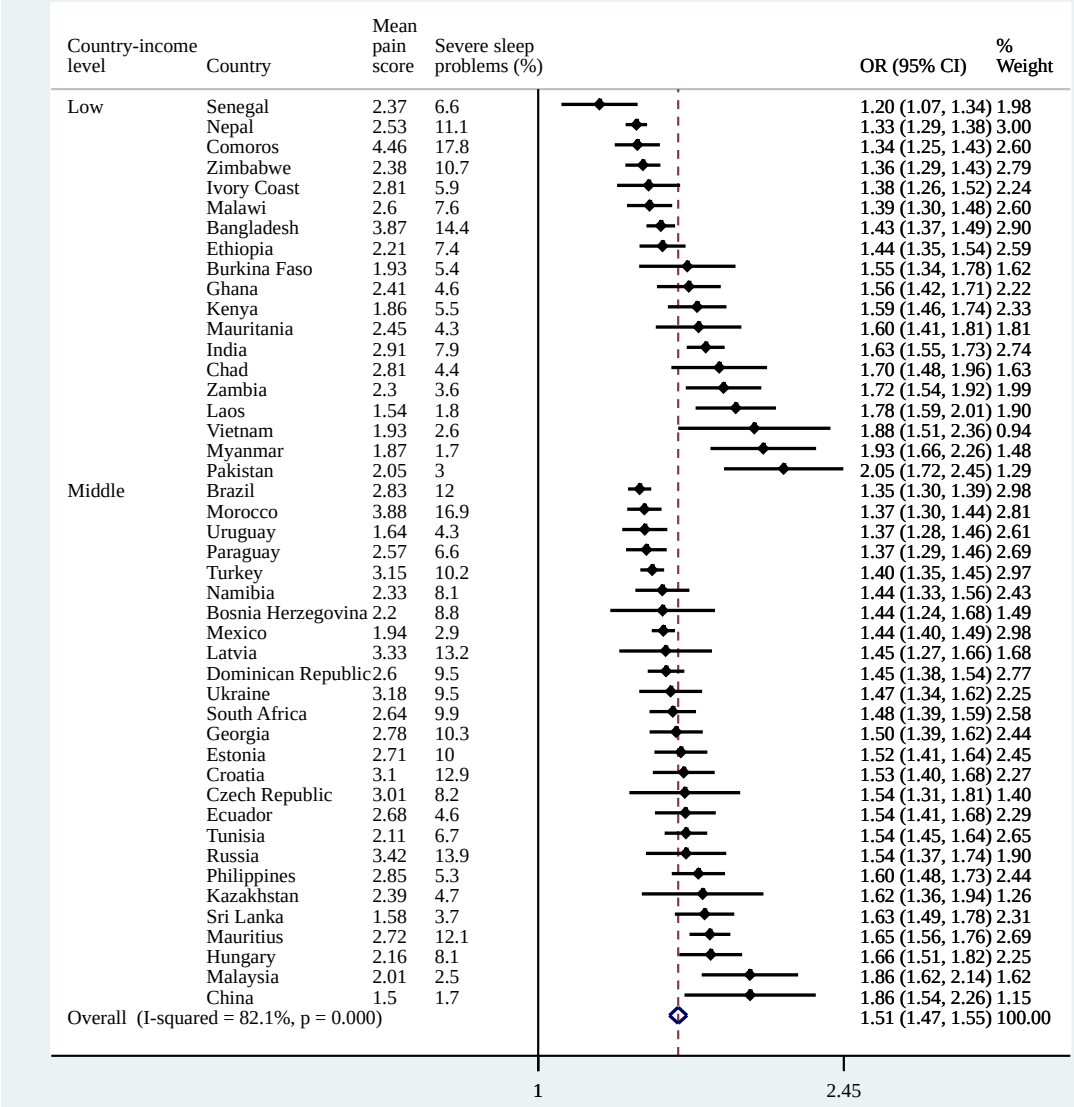


Figure 2 Country-wise association between pain score and severe sleep problems (outcome) estimated by age- and sex-adjusted logistic regression in 45 countries

Abbreviation: OR odds ratio; CI confidence interval

The pain score ranged from 0-10 with higher scores corresponding to higher levels of pain.

Overall estimate was obtained by meta-analysis with random effects.

References

1. Reimer MA, Flemons WW. Quality of life in sleep disorders. *Sleep Med Rev.* 2003;7(4):335-349.
2. Ferrie JE, Kumari M, Salo P, Singh-Manoux A, Kivimaki M. Sleep epidemiology--a rapidly growing field. In: *Int J Epidemiol.* Vol 40. England2011:1431-1437.
3. Brown W. Insomnia: prevalence and daytime consequences. In. In: Lee-Chiong T (ed.). Sleep: A

Comprehensive Handbook. Hoboken, NJ: John Wiley and
Sons, 2006,

pp. 93–98.

4. Mims KN, Kirsch D. Sleep and Stroke. *Sleep Med Clin.* 2016;11(1):39-51.
5. Buxton OM, Marcelli E. Short and long sleep are positively associated with obesity, diabetes, hypertension, and cardiovascular disease among adults in the United States. *Soc Sci Med.* 2010;71(5):1027-1036.
6. Gallicchio L, Kalesan B. Sleep duration and mortality: a systematic review and meta-analysis. *J Sleep Res.* 2009;18(2):148-158.
7. Gangwisch JE, Heymsfield SB, Boden-Albala B, et al. Sleep duration as a risk factor for diabetes incidence in a large U.S. sample. *Sleep.* 2007;30(12):1667-1673.
8. Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. *J Pain.* 2013;14(12):1539-1552.
9. Sofi F, Cesari F, Casini A, Macchi C, Abbate R, Gensini GF. Insomnia and risk of cardiovascular disease: a meta-analysis. *Eur J Prev Cardiol.* 2014;21(1):57-64.
10. Blank M, Zhang J, Lamers F, Taylor AD, Hickie IB, Merikangas KR. Health correlates of insomnia symptoms and comorbid mental disorders in a nationally representative sample of US adolescents. *Sleep.* 2015;38(2):197-204.
11. Chung KH, Li CY, Kuo SY, Sithole T, Liu WW, Chung MH. Risk of psychiatric disorders in patients with chronic insomnia and sedative-hypnotic prescription: a nationwide population-based follow-up study. *J Clin Sleep Med.* 2015;11(5):543-551.
12. Paunio T, Korhonen T, Hublin C, et al. Poor sleep predicts symptoms of depression and disability retirement due to depression. *J Affect Disord.* 2015;172:381-389.
13. Elzahaf RA, Tashani OA, Unsworth BA, Johnson MI. The prevalence of chronic pain with an analysis of countries with a Human Development Index less than 0.9: a systematic review without meta-analysis. *Curr Med Res Opin.* 2012;28(7):1221-1229.
14. Wong WS, Fielding R. The co-morbidity of chronic pain, insomnia, and fatigue in the general adult population of Hong Kong: Prevalence and associated factors. *J Psychosom Res.* 2012;73(1):28-34.
15. Roy M, Piche M, Chen JI, Peretz I, Rainville P. Cerebral and spinal modulation of pain by emotions. *Proc Natl Acad Sci U S A.* 2009;106(49):20900-20905.

16. Koyanagi A, Stickley A. The Association between Sleep Problems and Psychotic Symptoms in the General Population: A Global Perspective. *Sleep.* 2015;38(12):1875-1885.
17. Koyanagi A, Stickley A. The association between psychosis and severe pain in community-dwelling adults: Findings from 44 low- and middle-income countries. *Journal of psychiatric research.* 2015;69:19-26.
18. Bliwise DL. Invited commentary: cross-cultural influences on sleep--broadening the environmental landscape. *Am J Epidemiol.* 2008;168(12):1365-1366.
19. Bixler E. Sleep and society: an epidemiological perspective. *Sleep Med.* 2009;10 Suppl 1:S3-6.
20. Mazzotti DR, Guindalini C, Sosa AL, Ferri CP, Tufik S. Prevalence and correlates for sleep complaints in older adults in low and middle income countries: a 10/66 Dementia Research Group study. *Sleep Med.* 2012;13(6):697-702.
21. Nuevo R, Chatterji S, Verdes E, Naidoo N, Arango C, Ayuso-Mateos JL. The continuum of psychotic symptoms in the general population: a cross-national study. *Schizophrenia bulletin.* 2012;38(3):475-485.
22. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet.* 2007;370(9590):851-858.
23. Stranges S, Tigbe W, Gomez-Olive FX, Thorogood M, Kandala NB. Sleep problems: an emerging global epidemic? findings from the INDEPTH WHO-SAGE study among more than 40,000 older adults from 8 countries across Africa and Asia. *Sleep.* 2012;35(8):1173-1181.
24. Koyanagi A, Garin N, Olaya B, et al. Chronic Conditions and Sleep Problems among Adults Aged 50 years or over in Nine Countries: A Multi-Country Study. *PloS one.* 2014;9(12):e114742.
25. Koyanagi A, Oh H, Stickley A, Haro JM, DeVylder J. Risk and functional significance of psychotic experiences among individuals with depression in 44 low- and middle-income countries. *Psychological medicine.* 2016;in press.
26. Nuevo R, Van Os J, Arango C, Chatterji S, Ayuso-Mateos JL. Evidence for the early clinical relevance of hallucinatory-delusional states in the general population. *Acta psychiatrica Scandinavica.* 2013;127(6):482-493.
27. Rose GA. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bull World Health Organ.* 1962;27:645-658.
28. Boakye PA, Olechowski C, Rashiq S, et al. A Critical Review of Neurobiological Factors Involved in the Interactions Between Chronic Pain, Depression, and Sleep Disruption. *Clin J Pain.* 2016;32(4):327-336.
29. Kredlow MA, Capozzoli MC, Hearon BA, Calkins AW, Otto MW. The effects of physical activity on sleep: a meta-analytic review. *J Behav Med.* 2015;38(3):427-449.
30. Ghodse H. Pain, anxiety and insomnia--a global perspective on the relief of suffering: comparative review. *Br J Psychiatry.* 2003;183:15-21.
31. Wong KO, Hunter Rowe B, Douwes J, Senthilselvan A. Asthma and wheezing are associated with depression and anxiety in adults: an analysis from 54 countries. *Pulm Med.* 2013;2013:929028.
32. DeVylder JE, Koyanagi A, Unick J, Oh H, Nam B, Stickley A. Stress Sensitivity and Psychotic Experiences in 39 Low- and Middle-Income Countries. *Schizophrenia bulletin.* 2016:sbw044.

33. Craig CL, Marshall AL, Sjöström M, et al. International Physical Activity Questionnaire: 12-country reliability and validity... including commentary by Bassett DR Jr. *Medicine & Science in Sports & Exercise.* 2003;35(8):1381-1396.
34. Guthold R, Ono T, Strong KL, Chatterji S, Morabia A. Worldwide variability in physical inactivity a 51-country survey. *American journal of preventive medicine.* 2008;34(6):486-494.
35. Breen R, Karlson KB, Holm A. Total, Direct, and Indirect Effects in Logit and Probit Models. *Sociological Methods & Research.* 2013;42(2):164-191.
36. Koyanagi A, Stickley A, Haro JM. Subclinical psychosis and pain in an English national sample: The role of common mental disorders. *Schizophrenia research.* 2016.
37. Villemure C, Bushnell MC. Cognitive modulation of pain: how do attention and emotion influence pain processing? *Pain.* 2002;95(3):195-199.
38. Wiech K, Tracey I. The influence of negative emotions on pain: behavioral effects and neural mechanisms. *Neuroimage.* 2009;47(3):987-994.
39. Doufas AG, Panagiotou OA, Ioannidis JP. Concordance of sleep and pain outcomes of diverse interventions: an umbrella review. *PLoS One.* 2012;7(7):e40891.
40. Size M, Soyannwo OA, Justins DM. Pain management in developing countries. *Anaesthesia.* 2007;62 Suppl 1:38-43.
41. Campbell CM, Edwards RR. Ethnic differences in pain and pain management. *Pain Manag.* 2012;2(3):219-230.
42. Uchida S, Shioda K, Morita Y, Kubota C, Ganeko M, Takeda N. Exercise effects on sleep physiology. *Front Neurol.* 2012;3:48.
43. Tang NK, Lereya ST, Boulton H, Miller MA, Wolke D, Cappuccio FP. Nonpharmacological Treatments of Insomnia for Long-Term Painful Conditions: A Systematic Review and Meta-analysis of Patient-Reported Outcomes in Randomized Controlled Trials. *Sleep.* 2015;38(11):1751-1764.